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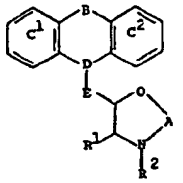
(19)

(54) MORPHOLINE DERIVATIVES AND PROCESSES FOR THE PRODUCTION THEREOF

(71) We, SUMITOMO CHEMICAL COMPANY LIMITED, a Japanese Body Corporate, of No. 15, Kitahama 5-chome, Higashi-ku, Osaka-shi, Osaka-fu, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

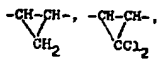
The present invention relates to novel morpholine derivatives and their production and use.

The morpholine derivatives of the present invention are morpholine compounds of the formula:



[I]

wherein R^1 is a hydrogen atom or a C_1—C_4 alkyl group, R^2 is a hydrogen atom, a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl (C_1—C_4)alkyl, (C_3—C_6)cycloalkyl(C_1—C_4) alkyl, polyhalo (C_2—C_4)alkyl or hydroxy(C_2—C_4) alkyl group, A is a straight or branched chain C_2—C_4 alkylene group, B is —CH_2—CH_2—, —CH=CH—,



—CH_2—O—, —CH_2—S—, —S— or —O—, >D—E— is >CH—CH_2— or >C=CH— and C^1 and C^2 are each 1,2-phenylene groups optionally substituted with one or more halogen atoms, C_1—C_4 alkyl or C_1—C_4 alkoxy groups, and their non-toxic salts.

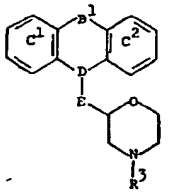
Examples of "C_1—C_4 alkyl" groups are methyl, ethyl, *n*-propyl, isopropyl and *n*-butyl. Examples of "C_3—C_5 alkenyl" groups are allyl and 3,3-dimethylallyl. Examples of "C_3—C_5 alkynyl" groups are propargyl and butynyl. Examples of "aryl-(C_1—C_4) alkyl" are benzyl and phenethyl. Examples of "(C_3—C_6)cycloalkyl-(C_1—C_4)alkyl" are cyclopropylmethyl and cyclopropylethyl. Examples of polyhalo-(C_2—C_4) alkyl" are trifluoroethyl and difluoroethyl. Examples of "hydroxy(C_2—C_4) alkyl" are hydroxyethyl and hydroxypropyl. Examples of "C_1—C_4 alkoxy" are methoxy and ethoxy. Examples of "straight or branched chain C_2—C_4 alkylene" are ethylene, propylene and isopropylene. Examples of "halogen" are fluorine, chlorine and bromine.

The morpholine compounds of formula [I] may form acid addition salts (e.g. hydrochloride, hydrobromide, sulfate, acetate, oxalate, citrate, succinate, fumarate, lactate) and quaternary ammonium salts (e.g. methochloride, methiodide).

The morpholine compounds [I] and their non-toxic salts exhibit pharmacological properties and accordingly are useful as pharmaceuticals. In general, they affect the functioning of the central nervous system. That is, they antagonize the central nervous system depressant effect induced by tetrabenazine and by reserpine, and also potentiate the central action of norepinephrine. Therefore, they are useful as antidepressants. Moreover, the acute toxicity and the acute cardio-toxicity of these compounds are relatively low, compared with those of standard antidepressants.

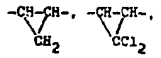
The present invention thus includes within its scope a pharmaceutical composition which comprises at least one compound of formula I, or a pharmaceutically acceptable salt thereof, together with a diluent or carrier.

Among the morpholine compounds [I] of the present invention, those of the following formula are preferable:



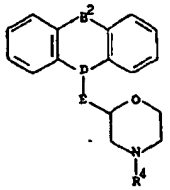
[I']

wherein B^1 is $-CH_2-CH_2-$, $-CH=CH-$,



$-CH_2-O-$ or $-CH_2-S-$, R^3 is a hydrogen atom, a C_1-C_3 alkyl, or allyl, propargyl, benzyl, cyclopropylmethyl, 2,2,2-trifluoroethyl or 2-hydroxyethyl and $>D-E-$, C^1 and C^2 are each as defined above, and their non-toxic salts.

The compounds of the following formula are particularly preferable:



[I'']

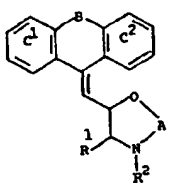
wherein B^2 is $-CH_2-CH_2-$, $-CH=CH-$ or

R^4 is a hydrogen atom or a C_1-C_3 alkyl group (preferably methyl) and $>D-E-$ is as defined above, and their non-toxic salts.

The morpholine compounds [I] and their non-toxic salts can be administered parenterally or orally with dosage adjusted to individual requirements (10—300 mg/human body (60 kg of body weight)/day) in the form of conventional pharmaceutical preparations. For instance, they may be administered in the form ow a conventional solid pharmaceutical preparation, such as tablets or capsules, or in the form of a conventional liquid pharmaceutical preparation, such as suspensions, emulsions or solutions.

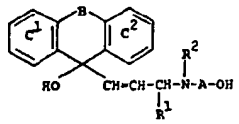
The morpholine compounds [I] may be prepared, for example, by the following methods.

(a) The morpholine compound of the formula:



[Ia]

wherein R^1, R^2, A, B, C^1 and C^2 are each as defined above can be prepared by subjeting an allylaminoalcohol of the formula:

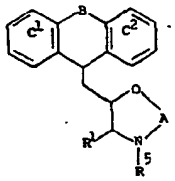


[II]

wherein R^1, R^2, A, B, C^1 and C^2 are each as defined above to acid-catalyzed rearrangement, followed by intramolecular cyclization.

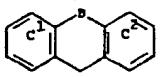
The rearrangement and cyclization may be carried out by treating compound II with an acid in the presence or absence of an inert solvent such as acetic acid, chloroform, *n*-hexane, diethyl ether or benzene. Examples of suitable acid are inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, polyphosphoric acid), organic strong acids (e.g. methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, oxalic acid, formic acid, trifluoroacetic acid) and Lewis acids (e.g. aluminum chloride, boron trifluoride). The temperature at which the reaction is carried out may vary from ice-cooling to reflux temperature.

(b) The morpholine compound of the formula:



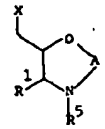
[Ib]

wherein R^5 is a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl(C_1—C_4)alkyl or (C_3—C_6) cycloalkyl(C_1—C_4)alkyl group and R^1, A, B, C^1 and C^2 are each as defined above can be prepared by reacting the tricyclic compound of the formula:



[III]

wherein B, C^1 and C^2 are each as defined above with the morpholinomethyl compound of the formula:

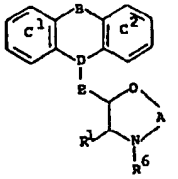


[IV]

wherein X is a suitable leaving group such as a halogen atom (e.g. chlorine or bromine) or a sulfonyloxy group (e.g. —OSO_2R^{12} wherein R^{12} is a hydroxyl, C_1—C_3 alkyl, polyhalo (C_1—C_3) alkyl, aryl, C_1—C_3 alkoxy or aryloxy group) and R^1, R^5 and A are each as defined above.

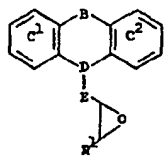
The reaction is usually carried out in an inert solvent such as benzene, toluene, xylene, diethyl ether, tetrahydrofuran, dioxane, dimethylformamide or dimethylsulfoxide in the presence of a base such as a metal amide (e.g. sodium amide or potassium amide), a metal hydride (e.g. sodium hydride) or an alkyl or aryl metal (e.g. *n*-butyl lithium or phenyl lithium). The temperature at which the reaction is carried out may vary from dry-ice-cooling to reflux temperature.

(c) The morpholine compound of the formula:



[Ic]

wherein R^6 is a hydrogen atom, a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl-(C_1—C_4) alkyl, (C_3—C_6)cycloalkyl(C_1—C_4) alkyl or polyhalo[C_2—C_4)alkyl group and R^1, A, B, >D—E—, C^1 and C^2 are each as defined above can be prepared by reacting an epoxide of the formula:



[V]

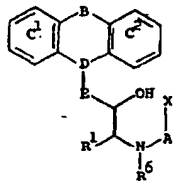
wherein R^1, B, >D—E—, C^1 and C^2 are each as defined above with the amine of the formula:

$$R^6—NH—A—X \qquad [VI]$$

wherein R^6, A and X are each as defined above, followed by treatment with a base.

The reaction of the epoxide [V] with the amine [VI] is usually carried out in an inert solvent such as an alcohol (e.g. methanol, ethanol, isopropanol or ethyleneglycol), an ether (e.g. diethylether, tetrahydrofuran or dioxane), an aromatic hydrocarbon (e.g. benzene or toluene) or mixtures thereof in the presence of a base such as a metal hydroxide (e.g. sodium hydroxide, potassium hydroxide or barium hydroxide) at a temperature ranging from room temperature to the reflux temperature of the reaction system.

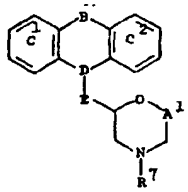
The reaction product is an aminoalcohol of the formula:



[VII]

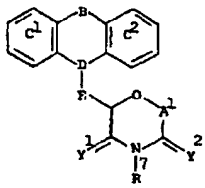
wherein R^1, R^6, A, B, >D—E—, C^1, C^2 and X are each as defined above, which is then subjected to treatment with a base, with or without the previous separation from the reaction mixture. The treatment may be carried out at a temperature from ice-cooling to the reflux temperature of the reaction system. The base may be a metal hydroxide (e.g. sodium hydroxide, potassium hydroxide or barium hydroxide), which is usually employed in an equimolar amount or more. The use of an inert solvent such as methanol, ethanol, tetrahydrofuran, dioxane, benzene, or toluene is normally preferred.

(d) The morpholine compound of the formula:



[Id]

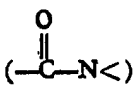
wherein R^7 is a hydrogen atom, a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl-(C_1—C_4)alkyl, (C_5—C_6)cycloalkyl(C_1—C_4)alkyl or hydroxy(C_2—C_4)alkyl group, A^1 is a straight or branched chain C_1—C_3 alkylene group and B, >D—E—, C^1 and C^2 are each as defined above can be prepared by reduction of the lactam of the formula:



[VIII]

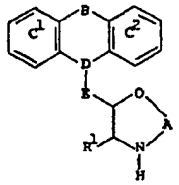
wherein A^1, B, R^7, >D—E—, C^1 and C^2 are each as defined above, Y^1 is an oxygen atom or two hydrogen atoms and Y^2 is an oxygen atom when Y^1 is two hydrogens or Y^2 is two hydrogen atoms when Y^1 is oxygen.

The reduction may be accomplished by the use of a reducing agent which is conventionally employed for reduction of a lactam



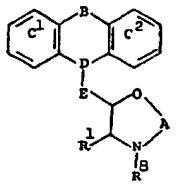
to an amine (—CH_2—N<). One of the most preferred reducing agents is a metal hydride, such as lithium aluminum hydride, sodium bis (2-methoxyethoxy)-aluminum hydride or sodium dihydrodiethyl aluminate. The reducing agent may be used in an equimolar amount or more to the compound [VIII]. When using sodium borohydride as the reducing agent, the presence of a salt such as aluminum chloride is favored. An inert solvent, such as an ether (e.g. diethyl ether, tetrahydrofuran, dioxane, ethyleneglycol dimethyl ether), an aliphatic hydrocarbon (e.g. heptane, n-hexane, cyclohexane) or an aromatic hydrocarbon (e.g. benzene, toluene) may be, if desired be employed in the reduction. The temperature for the reduction may vary from ice-cooling to the reflux temperature of the reduction system.

(e) The morpholine compound of the formula:



[Ie]

wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 can be prepared from the morpholine compound of the formula:



[IX]

wherein R^8 is a C_1—C_4 alkyl or aryl(C_1—C_4)alkyl group and R^1, A, B, >D—E—, C^1 and C^2 are each as defined above by substitution of R^8 with hydrogen.

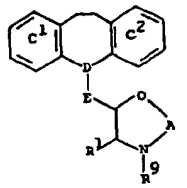
One of the most useful procedures for the substitution is the reaction of compound [IX] with an alkyl or aryl chloroformate (e.g. methyl chloroformate, ethyl chloroformate or phenyl chloroformate), followed by hydrolysis of the resulting alkoxycarbonyl or aryloxycarbonyl compound. The reaction with the alkyl or aryl chloroformate may be carried out at a temperature of from room temperature to the reflux temperature of the system in an inert solvent (e.g. benzene or toluene). The hydrolysis of the resulting alkoxycarbonyl or aryloxycarbonyl compound usually carried out in an inert solvent (e.g. water, hydrous methanol, hydrous ethanol) in the presence of a base such as a metal hydroxide (e.g. sodium hydroxide, potassium hydroxide) at a temperature of from room temperature to reflux temperature.

Another useful procedure for the substitution, which is particularly applicable to the production of compound [Ie] wherein B is other than —CH=CH— from the corresponding compound [IX] wherein R^8 is benzyl, is catalytic hydrogenation. The catalytic hydrogenolysis may be carried out in the presence of a catalyst such as palladium-on-charcoal under an atmosphere of hydrogen gas in an inert solvent such as an alcohol (e.g. methanol or ethanol). The hydrogen pressure can be 1 atmosphere or higher, and the temperature may be room temperature or higher. The presence of an acid (e.g. hydrochloric acid, acetic acid) in the reduction system generally promotes the progress of the reaction.

The compound [Ie] wherein B is —CH_2—CH_2— can also be prepared by cata-

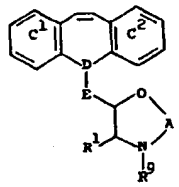
lytic hydrogenation and hydrogenolysis of the compound [IX] wherein B is —CH = CH— and R^8 is benzyl under the same condition as above.

(f) The morpholine compound of the formula:



[If]

wherein R^9 is a hydrogen atom, a C_1—C_4 alkyl, aryl(C_1—C_4) alkyl, (C_3—C_6)cycloalkyl(C_1—C_4)alkyl, polyhalo(C_2—C_4)alkyl or hydroxy(C_2—C_4)alkyl group and R^1, A, >D—E—, C^1 and C^2 are each as defined can be prepared by catalytic hydrogenation of the morpholine compound of the formula:

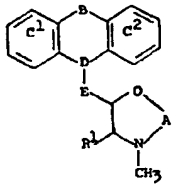


[X]

wherein R^1, A, >D—E—, R^9, C^1 and C^2 are each as defined above.

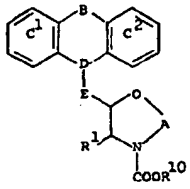
The catalytic hydrogenation may be carried out in the presence of a catalyst such as palladium-on-charcoal under an atmosphere of hydrogen gas in an inert solvent such as an alcohol (e.g. methanol or ethanol). The hydrogen pressure can be 1 atmosphere or higher, and the temperature may be room temperature or higher.

(g) The morpholine compound of the formula:



[Ig]

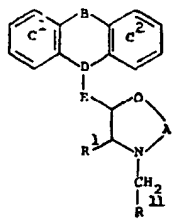
wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined above can be prepared by reducing the morpholine compound of the formula:



[XI]

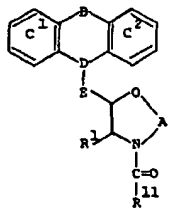
wherein R^{10} is C_1—C_4 alkyl or aryl and R^1, A, B, >D—E—, C^1 and C^2 are each as defined above. The reduction may be carried out in the substantially same manner as in Method (d).

(h) The morpholine compound of the formula:



[Ih]

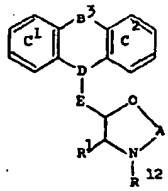
wherein R^{11} is a hydrogen atom, a C_1—C_3 alkyl, C_2—C_4 alkenyl, C_2—C_4 alkynyl, (C_3—C_6)cycloalkyl(C_1—C_3)alkyl, (C_3—C_6)cycloalkyl, aryl(C_1—C_3)alkyl, hydroxy-(C_1—C_3)alkyl or aryl group and R^1, A, B, >D—E—, C^1 and C^2 are each as defined above can be prepared by reducing the morpholine compound of the formula:



[XII]

wherein R^1, A, B, >D—E—, R^{11}, C^1 and C^2 are each as defined above. The reduction may be carried out in the substantially same manner as in Method (d).

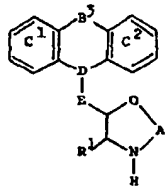
(i) The morpholine compound of the formula:



[Ii]

wherein R^{12} is a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl(C_1—C_4)alkyl, (C_3—C_6)cycloalkyl(C_1—C_4)alkyl, polyhalo(C_2—C_4)alkyl or hydroxy(C_2—C_4)alkyl group, B^3 is —CH_2—CH_2—, —CH=CH—,

—CH_2—O—, —CH_2—S—, —S— or —O— and R^1, A, >D—E—, C^1 and C^2 are each as defined above can be prepared by condensation of the morpholine compound of the formula:



[XIII]

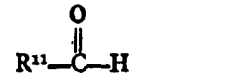
wherein R^1, A, B^3, >D—E—, C^1 and C^2 are each as defined above with a compound of the formula:

$$Z—R^{12} \qquad \text{[XIV]}$$

wherein Z is a suitable leaving group such as a halogen atom (e.g. chlorine or bromine) or sulfonyloxy (e.g. methanesulfonyloxy, *p*-toluenesulfonyloxy or trichloromethanesulfonyloxy) and R^{12} is as defined above.

The condensation may be effected in an inert solvent such as an aromatic hydrocarbon (e.g. benzene, toluene or xylene), dimethylformamide, dimethylsulfoxide or an alcohol (e.g. methanol, ethanol or propanol) in the presence of a base. Examples of suitable bases are a metal carbonate (e.g. sodium carbonate or potassium carbonate), a metal bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate), a metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), a metal hydride (e.g sodium hydride or potassium hydride), an alkylamine (e.g. triethylamine) or a metal alkoxide (e.g. sodium methoxide or sodium ethoxide). The base may be used in a stoichiometric amount or more. The temperature for the condensation may vary from room temperature to reflux temperature.

(j) The morpholine compound [Ih] can be prepared by condensation-reduction of the corresponding morpholine compound [Ie] with a carbonyl compound of the formula:



[XV]

wherein R^{11} is as defined above.

The condensation-reduction may be accomplished by procedures known *per se*. The usual procedure of Leuckart-Wallach reaction using formic acid is applicable to the condensation-reduction [Organic Reactions, Vol. 5, p. 301, John Wiley & Sons, Inc.]. For instance, the compound [XV] is added to a mixture of the amineformate of the compound [Ie] and formic acid, and the resultant mixture is heated at a temperature from room temperature to 200°C.

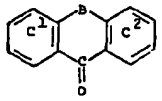
The condensation-reduction can be also effected by hydrogenation of a mixture of the compound [Ic] and the compound [XV] over a catalyst such as Raney nickel, platinum oxide or palladium in the presence or absence of an inert solvent. The pressure may be 1 atmosphere or higher. A condensation agent such as sodium acetate may be used.

The condensation-reduction can be further accomplished by using the sodium-alcohol or zinc-acid or alkali method. Examples of inert solvents for use in the reaction are alcohols (e.g. methanol, ethanol, isopropanol), liquid ammonia, acetic acid and ethers (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane).

Moreover, the condensation-reduction can be accomplished by the reduction of the Schiff base or enamine prepared from the compound [Ie] and the compound [XV] by a conventional method. The reduction may be performed in the same manner as the hydrogenation procedure described above. A reducing agent such as sodium borohydride, diborane, lithium aluminum hydride, sodium aluminum diethyldihydride, sodium borocyanohydride or bis(2-methoxyethoxy-aluminum hydride can be used in the reduction in an inert solvent such as an alcohol (e.g. methanol, ethanol, *iso*-propanol, *n*-butanol or *t*-butanol), an aromatic hydrocarbon (e.g. benzene or toluene) or an ether (e.g. diethyl ether, diisopropyl ether, dioxane or tetrahydrofuran). The temperature for the treatment in this case can be varied from −10°C to the reflux temperature.

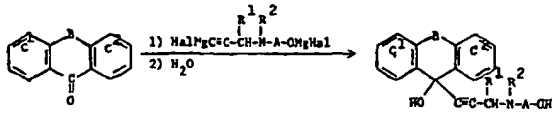
The morpholine compounds I prepared according to the above processes can be converted into their salts by conventional techniques, and reconversion from the salts to the original free bases can be also carried out in conventional manner.

The intermediate tricyclic allylaminoalcohol II, for example, can be prepared from the tricyclic carbonyl compound of the formula:

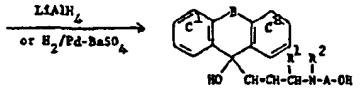


[XVI]

wherein B, C^1 and C^2 are each as defined above according to the following steps:



[XVI] [XVII]



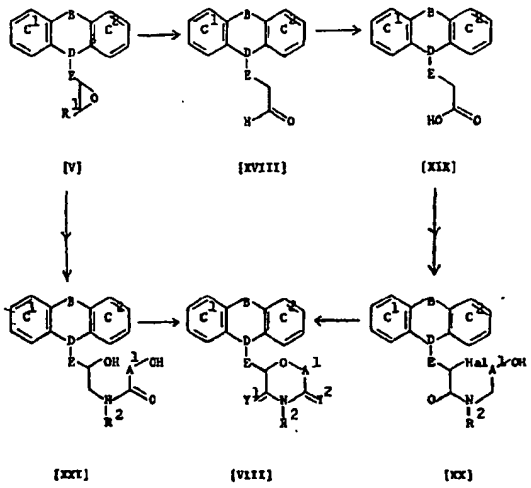
[II]

wherein Hal is halogen (e.g. chlorine, bromine or iodine) and R^1, R^2, A, B, C^1 and C^2 are each as defined above.

The first step is the Grignard reaction of the tricyclic carbonyl compound [XVI] with an acetylenic Grignard reagent in an inert solvent. The second step is the partial reduction of the resulting tricyclic propargylaminoalcohol ;XVII] with a metal hydride such as lithium aluminum hydride or hydrogen in the presence of a metal catalyst such as palladium on barium sulfate.

The intermediate epoxide [V], for example, can be prepared by a known method as described in Dutch Patent Application No. 66.05979.

The intermediate lactam [VIII], for example, can be prepared from the epoxide [V] wherein R^1 is hydrogen, according to the following steps:



wherein R^1 is a hydrogen atom and R^2, A^1, B, >D—E—, C^1, C^2, Y^1, Y^2 and Hal are each as defined above.

The lactam [VIII] wherein Y^1 is two hydrogen atoms and Y^2 is an oxygen atom, for example, can be prepared from the epoxide [V] via the amide [XXI]. The first step is the amination of the epoxide [V], followed by acylation of the resulting amino-alcohol with an acylating agent. The second step is the intramolecular dehydration of the resulting amide [XXI] in the presence of an acid.

The lactam [VIII] wherein Y^1 is an oxygen atom and Y^2 is two hydrogen atoms, for example, can be prepared from the epoxide [V] via the aldehyde [XVIII], the carboxylic acid [XIX] and the amide [XX]: The first step is the isomerization of the epoxide [V] in the presence of an acid such as boron trifluoride-etherate. The second step is the halogenation of the carboxylic acid [XIX] followed by the amidation of the resulting halocarboxylic acid. The third step is the intramolecular dehydrohalogenation of the halo-amide [XX] in the presence of a base.

The following examples are given to illustrate the present invention.

Example 1.

Concentrated hydrochloric acid (7 ml) was added to a solution of N - benzyl-N - [3 - (10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - yl)allyl] - 2 - ethanol-amine (490 mg) in glacial acetic acid under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours. fter the reaction mixture was evaporated to dryness under reduced pressure, the residue was neutralized with 10% aqueous sodium hydroxide solution and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to afford 5 - (4 - benzylmorpholin-2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 209—210°C (decomp.) (oxalate).

Example 2.

A solution of n-butyl lithium in n-hexane (1.6 N, 1.6 ml) was added to 10,11-dihydro - 5H - dibenzo[a,d]cycloheptene (390 mg) in anhydrous tetrahydrofuran at room temperature, and the resulting mixture was stirred under reflux for 40 minutes. A solution of 2 - chloromethyl - 4 - isopropylmorpholine (362 mg) in benzene was added thereto while stirring under heating, and the resulting mixture was stirred under

reflux for 4 hours, followed by addition of excess water. The reaction mixture was extracted with ethyl acetate. The ethyl acetate extract was dried, evaporated and chromatographed to afford 5 - (4 - isopropylmorpholin - 2 - yl)methyl - 10,11-dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 219—221°C (hydrochloride).

Example 3.

Ethyl chloroformate (3.6 g) was added to 5 - (4 - benzylmorpholin - 2 - yl)-methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene (3.13 g) in anhydrous benzene at room temperature, and the resulting mixture was heated under reflux for 5.5 hours. After cooling, the mixture was washed with saturated aqueous sodium bicarbonate solution and water, dried and evaporated to afford 5 - (4 - ethoxycarbonylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material.

Potassium hydroxide (3.0 g) in water was added to above-obtained 5 - (4-ethoxycarbonylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]-cycloheptene (2.49 g) in ethanol, and the resulting mixture was heated under reflux for 8 hours. After cooling, ethanol was distilled off and water was added to the resulting residue. The resultant mixture was extracted with chloroform. The chloroform extract was dried, evaporated and chromatographed to afford 5 - (morpholin - 2 - yl)-methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 221—224°C (oxalate).

Example 4.

A solution of 5 - (4 - benzylmorpholin - 2 - yl)methylidene - 10,11 - dihydro-5H - dibenzo[a,d]cycloheptene (1.00 g) in isopropanol was added to 10% palladium on charcoal (265 mg) pretreated under hydrogen in hydrochloric acid, and the resulting mixture was stirred under hydrogen at room temperature for 12 hours. After elimination of the catalyst by filtration, the filtrate was evaporated. The residue was neutralized with 10% aqueous sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with water, dried and evaporated to afford 5-(morpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 221—224°C (oxalate).

Example 5.

A solution of 5 - (4 - benzylmorpholin - 2 - yl)methylidene - 5H - dibenzo-[a,d]cycloheptene (0.32 g) in acetic acid was added to 10% palladium on charcoal (90 mg) pretreated under hydrogen in hydrochloric acid, and the resulting mixture was stirred under hydrogen at room temperature for 8 hours. After elimination of the catalyst by filtration, the filtrate was evaporated. The residue was neutralized with 10% aqueous sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with water, dried and evaporated to afford 5 - (morpholin - 2 - yl)-methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 221—224°C (oxalate).

Example 6.

A solution of 5 - (morpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene (0.62 g) in methanol was added to 5% palladium on charcoal (400 mg) pretreated under hydrogen in methanol, and the resulting mixture was stirred under hydrogen at room temperature for 20 hours. After elimination of the catalyst by filtration, the filtrate was evaporated to afford 5 - (morpholin - 2 - yl)methylidene - 10,11-dihydro[a,d]cycloheptene as oily material. M.P., 221—224°C (oxalate).

Example 7.

To a solution of lithium aluminum hydride (155 mg) in anhydrous ether was added a solution of 5 - (4 - ethoxycarbonylmorpholin - 2 - yl)methylidene - 10,11-dihydro - 5H - dibenzo[a,d]cycloheptene (600 mg) in anhydrous ether under ice-cooling, and the resulting mixture was stirred under ice-cooling for 1 hour and under reflux for 2.5 hours. The reaction mixture was cooled, admixed with 10% aqueous sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to afford 5 - (4 - methylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 243—244°C (decomp.) (oxalate).

Example 8.

To a solution of lithium aluminum hydride (100 mg) in anhydrous ether was added a solution of 5 - (4 - acetylmorpholin - 2 - yl)methylidene - 10,11 - dihydro-5H - dibenzo[a,d]cycloheptene (350 mg) in anhydrous ether under ice-cooling, and the resulting mixture was stirred under reflux for 3 hours. The reaction mixture was cooled, admixed with 10% aqueous sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to afford 5 - (4 - ethylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]-cycloheptene as oily material. M.P., 224—225°C (oxalate).

Example 9.

To 5 - (morpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]-cycloheptene (300 mg) in ethanol were added propargyl bromide (2.0 g) and potassium hydroxide (570 mg) in water at room temperature, and the resulting mixture was stirred at room temperature for 1 hour. After ethanol was distilled off, water was added to the residue, and the resultant mixture was extracted with chloroform. The chloroform extract was dried, evaporated and chromatographed to afford 5 - (4 - propargylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as crystalline material. M.P., 124—125°C.

Example 10.

To 5 - (morpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]-cycloheptene (0.69 g) in anhydrous tetrahydrofuran was added sodium amide (0.20 g) at room temperature, and the resulting mixture was heated under reflux for 1.5 hours. After cooling, 2,2,2-trifluoroethyl trichloromethylsulfonate (0.666 g) in anhydrous tetrahydrofuran was added to the mixture under ice-cooling, and then the mixture was heated under reflux for 11.5 hours. After cooling, water (0.2 g) was added thereto and inorganic materials were eliminated by filtration. The filtrate was evaporated and chromatographed to afford 5 - [4 - (2,2,2 - trifluoroethyl)morpholin - 2 - yl]methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 174—177°C (hydrochloride).

Example 11.

A mixture of 5 - (morpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene (0.35 g), 90% formic acid (0.7 g) and 37% formalin (0.65 ml) was stirred at 95—100°C for 6.5 hours. After cooling, 4N hydrochloric acid was added thereto, and the resulting mixture was evaporated to dryness under reduced pressure, neutralized with ammonia water and extracted with benzene. The benzene extract was washed with water, dried over anhydrous sodium sulfate and evaporated to afford 5 - (4 - methylmorpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 237—238°C (decomp.) (oxalate).

Example 12.

To a suspension of lithium aluminum hydride (0.05 g) in anhydrous tetrahydrofuran (7 ml) was added a solution of 5 - (4 - benzyl - 5 - oxomorpholin - 2 - yl)-methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene (0.55 g) in anhydrous tetrahydrofuran (15 ml) under ice-cooling, and the resulting mixture was stirred at room temperature for one hour and refluxed with stirring for 7 hours. The reaction mixture was cooled, admixed with water and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to afford 5 - (4-benzylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene as oily material. M.P., 209—210°C (decomp.) (oxalate).

Example 13.

A mixture of 5 - (2,3 - epoxypropylidene) - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene (0.65 g), 2-aminoethyl hydrogensulfate (2.5 g) and sodium hydroxide (1.6 g) in water (8 ml) was stirred in ethanol (11 ml) under reflux for 15 hours. The reaction mixture was concentrated and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate and evaporated to afford 5 - (morpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]-cycloheptene as oily material. M.P., 221—224°C (oxalate).

The following compounds were produced by one or more procedures described above:

5 - (Morpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 221—224°C (oxalate);

5 - (Morpholin - 2 - yl)methyl - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 205—207°C (hydrochloride);
5 - (4 - Methylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 243—244°C (decomp.) (oxalate);
5 - (4 - Methylmorpholin - 2 - yl)methyl - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 188—189.5°C (hydrochloride);
5 - (4 - Benzylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 209—210°C (decomp.) (oxalate);
5 - (4 - Benzylmorpholin - 2 - yl)methyl - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 128—131°C (hydrochloride);
5 - (4 - Ethylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 224—225°C (decomp.) (oxalate);
5 - (4 - Cyclopropylmethylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H-dibenzo[a,d]cycloheptene, M.P., 195—198°C (hydrochloride);
5 - (4 - Isopropylmorpholin - 2 - yl)methyl - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 219—221°C (hydrochloride);
5 - (4 - Allylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 212—213°C (decomp.) (oxalate);
5 - (4 - Propargylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 124—125°C;
5 - [4 - (2 - Hydroxyethyl)morpholin - 2 - yl]methylidene - 10,11 - dihydro-5H - dibenzo[a,d]cycloheptene, M.P., 210—212°C (hydrochloride);
5 - [4 - (2,2,2 - Trifluoroethyl)morpholin - 2 - yl]methylidene - 10,11 - dihydro-5H - dibenzo[a,d]cycloheptene, M.P., 174—177°C (hydrochloride);
5 - (Morpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene, M.P., 224—226°C (decomp.) (oxalate);
5 - (Morpholin - 2 - yl)methyl - 5H - dibenzo[a,d]cycloheptene, M.P., 198.5—200°C (oxalate);
5 - (4 - Methylmorpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene, M.P., 237—238°C (decomp.) (oxalate);
5 - (4 - Benzylmorpholin - 2 - yl)methyl - 5H - dibenzo[a,d]cycloheptene, I.R. (neat): 3060, 3030, 1595, 1492, 1480, 1350, 1065, 1035, 850, 800, 765 and 700 cm^{-1};
5 - (4 - Isopropylmorpholin - 2 - yl)methyl - 5H - dibenzo[a,d]cycloheptene, M.P., 166—169°C (hydrochloride);
5 - (4 - Propargylmorpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene, M.P., 146—150°C (hydrochloride);
6 - (Morpholin - 2 - yl)methylidene - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene, M.P., 163—165°C (hydrochloride);
6 - (4 - Methylmorpholin - 2 - yl)methylidene - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene, M.P., 235—236°C (decomp.) (oxalate);
6 - (4 - Benzylmorpholin - 2 - yl)methylidene - 1,1a,6,10b - tetrahydrodibenzo[a,e,]cyclopropa[c]cycloheptene, M.P., 151—154°C (hydrochloride);
6 - (4 - Isopropylmorpholin - 2 - yl)methyl - 1,1a,6,10b - tetrahydrodibenzo[a,e,]cyclopropa[c]cycloheptene, M.P., 162—165°C (hydrochloride);
1,1 - Dichloro - 6 - (4 - benzylmorpholin - 2 - yl)methylidene - 1,1a,6,10b-tetrahydrodibenzo[a,e]cyclopropa[c]cycloheptene, I.R. (neat): 3060, 3020, 1650, 1600, 1570, 1490, 1455, 1100, 1065, 1020 and 745 cm^{-1}.
11 - (Morpholin - 2 - yl)methylidene - 6,11 - dihydrodibenzo[b,e]oxepin, M.P., 207—210°C (oxalate);
11 - (4 - Methylmorpholin - 2 - yl)methylidene - 6,11 - dihydrodibenzo[b,e]-oxepin, M.P., 120—121°C (oxalate);
11 - (4 - Benzylmorpholin - 2 - yl)methylidene - 6,11 - dihydrodibenzo[b,e]-oxepin, M.P., 153—155°C (decomp.) (oxalate);
11 - (4 - Methylmorpholin - 2 - yl)methylidene - 6,11 - dihydrodibenzo[b,e]thiepine, M.P., 122—123°C (oxalate);
9 - (Morpholin - 2 - yl)methylxanthene, M.P., 200—201°C (oxalate);
9 - (4 - Benzylmorpholin - 2 - yl)methylxanthene, I.R. (neat): 3060, 3020, 1605, 1585, 1485, 1465, 1115 and 765 cm^{-1};
2 - Chloro - 9 - (4 - methylmorpholin - 2 - yl)methylidenethioxanethen, I.R. (neat): 3050, 3000, 2780, 1620, 1580, 1555, 1540, 1450, 1105, 1095, 1065 and 750 cm^{-1};
9 - (4 - Isopropylmorpholin - 2 - yl)methylthioxanthene, M.P., 225—225.5°C (hydrochloride);
5 - (Hexahydro - 4 - methyl - 1,4 - oxazepin - 2 - yl)methylidene - 10,11-dihydro - 5H - dibenzo[a,d]cycloheptene, M.P., 188—190°C (oxalate);

6 - (4 - Benzylmorpholin - 2 - yl)methyl - 1,1a,6,10b - tetrahydrodibenzo[a,e]-cyclopropa[c]cycloheptene, M.P., 123—125°C;

6 - (Morpholin - 2 - yl)methyl - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa-[c]cycloheptene, M.P., 203—205°C (oxalate), etc.

Examples of other typical tricyclic morpholine derivatives provided by the invention are as follows:

5 - (4 - Isopropylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene;

5 - (4 - Methylmorpholin - 2 - yl)methyl - 5H - dibenzo[a,d]cycloheptene;

6 - (Morpholin - 2 - yl)methyl - 1,1a,6,10b - tetrahydrodibenzo[a,e]cyclopropa-[c]cycloheptene;

6 - (4 - Methylmorpholin - 2 - yl)methyl - 1,1a,6,10b - tetrahydrodibenzo[a,e]-cyclopropa[c]cycloheptene;

11 - (Morpholin - 2 - yl)methyl - 6,11 - dihydrodibenzo[b,e]oxepin;

11 - (4 - Methylmorpholin - 2 - yl)methyl - 6,11 - dihydrodibenzo[b,e]oxepin;

11 - (Morpholin - 2 - yl)methylidene - 6,11 - dihydrodibenzo[b,e]thiepin;

11 - (Morpholin - 2 - yl)methyl - 6,11 - dihydrodibenzo[b,e]thiepin;

11 - (4 - Methylmorpholin - 2 - yl)methyl - 6,11 - dihydrodibenzo[b,e]thicpin;

9 - (Morpholin - 2 - yl)methylidenexanthene;

9 - (Morpholin - 2 - yl)methylidenethioxanthene;

5 - (3 - Methylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene;

5 - (5 - Methylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene;

5 - (6 - Methylmorpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene;

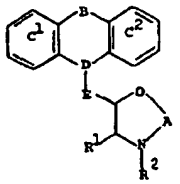
5 - [4 - (3,3 - Dimethylallyl)morpholin - 2 - yl]methylidene - 10,11 - dihydro-5H - dibenzo[a,d]cycloheptene;

1,1 - Dichloro - 6 - (morpholin - 2 - yl)methylidene - 1,1a,6,10b - tetrahydro-dibenzo[a,e]cyclopropa[c]cycloheptene;

1,1 - Dichloro - 6 - (4 - methylmorpholin - 2 - yl)methylidene - 1,1a,6,10b - tetra-hydrodibenzo[a,e]cyclopropa[c]cycloheptene.

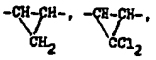
WHAT WE CLAIM IS:—

1. A compound of the formula:



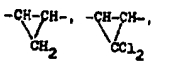
[I]

wherein R^1 is a hydrogen atom or a C_1—C_4 alkyl group, R^2 is a hydrogen atom, a C_1—C_4 alkyl, C_3—C_5 alkynyl, aryl(C_1—C_4)alkyl, (C_3—C_6)cycloalkyl(C_1—C_4)alkyl, polyhalo(C_2—C_4)alkyl or hydroxy(C_2—C_4) alkyl group, A is straight or branched chain C_2—C_4 alkylene group, B is $-CH_2-CH_2-$, $-CH=CH-$,



$-CH_2-O-$, $-CH_2-S-$, $-S-$ or $-O-$, $>D-E-$ is $>CH-CH_2-$ or $>C=CH-$ and C^1 and C^2 are each 1,2-phenylene groups optionally substituted with one or more halogen atoms, C_1—C_4 alkyl or C_1—C_4 alkoxy groups.

2. A compound as claimed in claim 1 wherein A is $-CH_2-CH_2-$, R^1 is hydrogen, B is $-CH_2-CH_2-$, $-CH=CH-$,



$-CH_2-O-$ or $-CH_2-S-$ and R^2 is a hydrogen atom, or C_1—C_3 alkyl, or allyl, propargyl, benzyl, cyclopropylmethyl, 2,2,2-trifluoroethyl or 2-hydroxvethyl group.

3. A compound as claimed in claim 2 wherein B is $-CH_2-CH_2-$, $-CH=CH-$ or

R^2 is a hydrogen atom or a C_1—C_3 alkyl group and C^1 and C^2 are each unsubstituted 1,2-phenylene groups.

4. A compound as claimed in claim 3 wherein R^2 is a hydrogen atom or a methyl group.

5. 5 - (Morpholine - 2 - yl)methylidene - 10,11 -dihydro - 5H - dibenzo[a,d]-cycloheptene.

6. 5 - (Morpholin - 2 - yl)methyl - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

7. 5 - (4 - Methylmorpholin - 2 - yl)methylidene - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

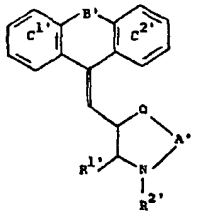
8. 5 - (4 - Methylmorpholin - 2 - yl)methyl - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene.

9. 5 - (Morpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene.

10. 5 - (4 - Methylmorpholin - 2 - yl)methylidene - 5H - dibenzo[a,d]cycloheptene.

11. 5 - (Morpholin - 2 - yl)methyl - 5H - dibenzo[a,d]cycloheptene.

12. A compound of the formula:



wherein

$R^{1'}$ is a hydrogen atom or a C_1—C_4 alkyl group,

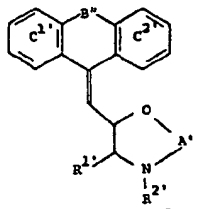
$R^{2'}$ is a hydrogen atom, a C_1—C_4 alkyl, lower alkenyl, aryl(C_1—C_4)alkyl or (C_3—C_6)cycloalkyl (C_1—C_4)alkyl group,

A' is a straight or branched C_2—C_3 alkylene chain,

B' is a —CH_2—CH_2— or —CH = CH— group, and

$C^{1'}$ and $C^{2'}$ are each a 1,2-phenylene group.

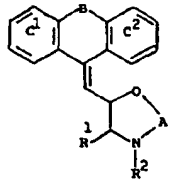
13. A compound of the formula:



wherein $R^{1'}$, $R^{2'}$, A', $C^{1'}$ and $C^{2'}$ are each as defined in claim 12 and B" is a —O—, —S—, —CH_2O— or —CH_2S— group.

14. A non-toxic salt of a compound as claimed in any one of the preceding claims.

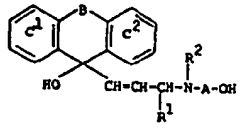
15. A process for preparing morpholine compounds of the formula:



[Ia]

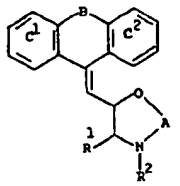
wherein R^1, R^2, A, B, >D—E, C^1 and C^2 are as defined in claim 1 and the non-toxic salts thereof which process comprises:

(a) subjecting an allylaminoalcohol of the formula:



[II]

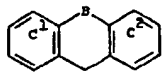
wherein R^1, R^2, A, B, C^1 and C^2 are each as defined in claim 1 to acid-catalyzed rearrangement, followed by intramolecular cyclization to give a compound of the formula:



[Ia]

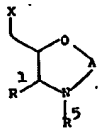
wherein R^1, R^2, A, B, C^1 and C^2 are each as defined above;

or (b) reacting the tricyclic compound of the formula:



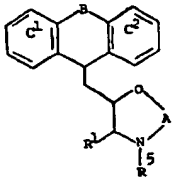
[III]

wherein B, C^1 and C^2 are each as defined in claim 1 with the morpholinomethyl compound of the formula:



[IV]

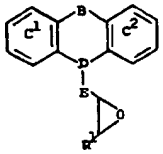
wherein X is a suitable leaving group, R^5 is a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl(C_1—C_4)alkyl or (C_3—C_6)cycloalkyl(C_1—C_4)alkyl group and R^1 and A are each as defined in claim 1 to give a compound of the formula:



[Ib]

wherein R^1, A, B, C^1 and C^2 are each as defined in claim 1 and R^5 is as defined above;

or (c) reacting the epoxide of the formula:

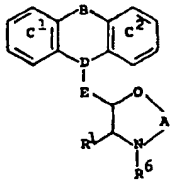


[V]

wherein R^1, B, >D—E—, C^1 and C^2 are each as defined in claim 1 with the amine of the formula:

$$R^6—NH—A—X$$

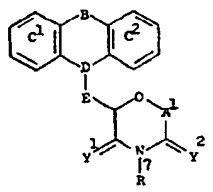
wherein R^6 is a hydrogen atom, a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl-(C_1—C_4)alkyl, (C_3—C_6)cycloalkyl(C_1—C_4) alkyl as polyhalo[C_2—C_4)alkyl group, A is as defined in claim 1 and X is a conventional leaving group followed by treatment with a base to give a compound of the formula:



[Ic]

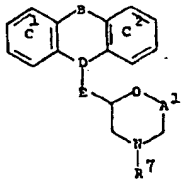
wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 and R^6 is as defined above;

(d) reducing the lactam of the formula:



[VIII]

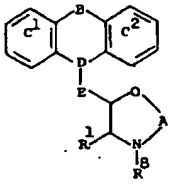
wherein R^7 is a hydrogen atom, a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl(C_1—C_4)alkyl, (C_3—C_6)cycloalkyl(C_1—C_4)alkyl or hydroxy(C_2—C_4)alkyl group, A^1 is a straight or branched chain C_1—C_3 alkylene group, Y^1 is an oxygen atom or two hydrogen atoms and Y^2 is an oxygen atom when Y^1 is two hydrogens or Y^2 is two hydrogen atoms when Y^1 is oxygen, and B, >D—E—, C^1 and C^2 are each as defined in claim 1 to give a compound of the formula:



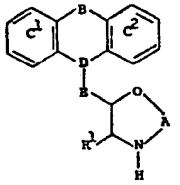
[Id]

wherein R^7 and A^1 are each as defined above and B, >D—E—, C^1 and C^2 are each as defined in claim 1;

or (e) (i) subjecting the morpholine compound of the formula:

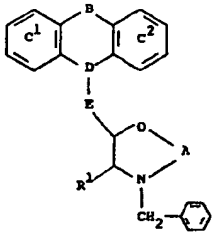


wherein R^6 is a C_1—C_4 alkyl or aryl(C_1—C_4)alkyl group and R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 to reaction with an alkyl or aryl formate, followed by hydrolysis of the resulting compound to give a compound of the formula:

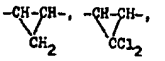


wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined above;

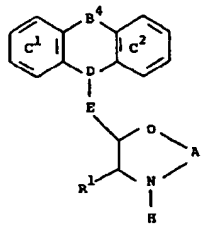
(ii) subjecting the morpholine compound of the formula:



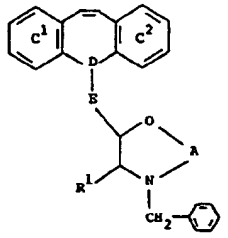
wherein B^4 is $-CH_2CH_2-$,



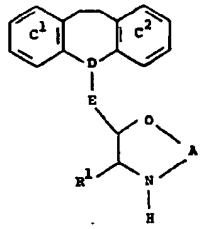
$-CH_2-O-$, $-CH_2-S-$, $-S-$ or $-O-$ and R^1, A, $>D-E-$, C^1 and C^2 are each as defined above to catalytic hydrogenolysis in the presence of an acid to give a compound of the formula:



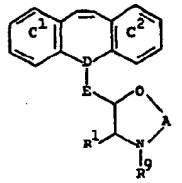
wherein R^1, A, B^4, $>D-E-$, C^1 and C^2 are each as defined above;
or (iii) subjecting the morpholine compound of the formula:



wherein R^1, A, $>D-E-$, C^1 and C^2 are each as defined above to catalytic hydrogenation and hydrogenolysis in the presence of an acid to give a compound of the formula:

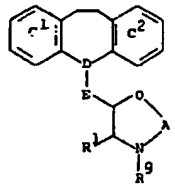


wherein R^1, A, $>D-E-$, C^1 and C^2 are each as defined above;
or (f) subjecting the morpholine compound of the formula:



[X]

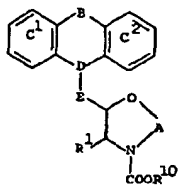
wherein R^9 is a hydrogen atom, a C_1-C_4 alkyl, aryl(C_1-C_4)alkyl, (C_3-C_6) cycloalkyl(C_1-C_4)alkyl, polyhalo(C_2-C_4)alkyl or hydroxy(C_2-C_4)alkyl group and R^1, A, $>D-E-$, C^1 and C^2 are each as defined in claim 1 to catalytic hydrogenation to give a compound of the formula:



[It]

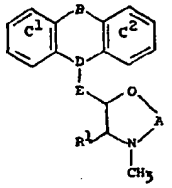
wherein R^1, A, >D—E—, C^1 and C^2 are each as defined in claim 1 and R^9 is as defined above:

or (g) reducing the morpholine compound of the formula:



[XI]

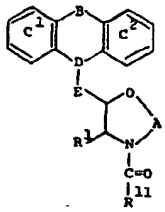
wherein R^{10} is C_1—C_4 alkyl or aryl and R^1, A, B, >D—E—, C^1 and C^2 are each as defined above to give a compound of the formula:



[Ig]

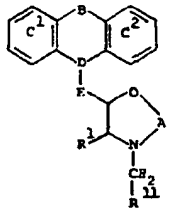
wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1;

or (h) reducing the morpholine compound of the formula:



[XII]

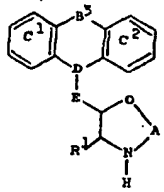
wherein R^{11} is a hydrogen atom, a C_1—C_3 alkyl, C_2—C_4 alkenyl, C_2—C_4 alkynyl, (C_3—C_6)cycloalkyl(C_1—C_3)alkyl, (C_3—C_6) cycloalkyl, aryl(C_1—C_3)alkyl, hydroxy-(C_1—C_3)alkyl or aryl group and R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 to give a compound of the formula:



[Ih]

wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 and R^{11} is as defined above;

or (i) condensing the morpholine compound of the formula:



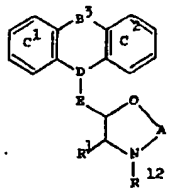
[XIII]

wherein B^1 is —CH_2—CH_2—, —CH=CH—,

—CH_2—O—, —CH_2—S—, —S— or —O— and R^1, A, >D—E—, C_1 and C_2 are each as defined above with a compound of the formula:

$$Z—R^{12}$$

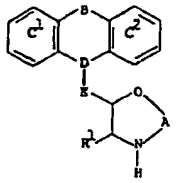
wherein Z is a suitable leaving group and R^{12} is a C_1—C_4 alkyl, C_3—C_5 alkenyl, C_3—C_5 alkynyl, aryl(C_1—C_4)alkyl, (C_3—C_6)cycloalkyl(C_1—C_4)alkyl, polyhalo-(C_2—C_4)alkyl or hydroxy(C_2—C_4)alkyl group to give a compound of the formula:



[Ii]

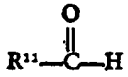
wherein R^1, A, >D—E—, C^1 and C^2 are each as defined in claim 1 and R^{12} and B^3 are each as defined above;

or (j) subjecting the morpholine compound of the formula:

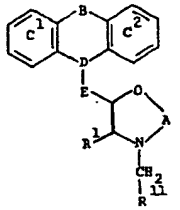


[Ie]

wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 and a carbonyl compound of the formula:



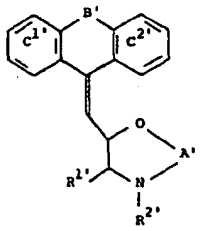
wherein R^{11} is as defined above to condensation-reduction to give a compound of the formula:



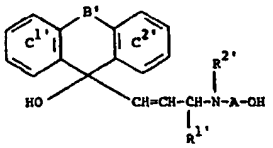
[Ih]

wherein R^1, A, B, >D—E—, C^1 and C^2 are each as defined in claim 1 and R^{11} is as defined above.

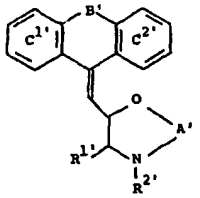
16. A process for preparing morpholine compounds of the formula:



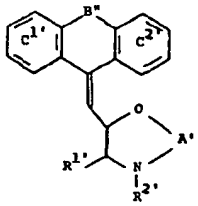
wherein $R^{1'}$, $R^{2'}$, A', B', $C^{1'}$ and $C^{2'}$ are each as defined in claim 12, which process comprises subjecting an allylamino-alcohol of the formula:



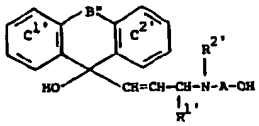
wherein $R^{1'}$, $R^{2'}$, A', B', $C^{1'}$ and $C^{2'}$ are as defined above to acid-catalyzed rearrangement, followed by intramolecular cyclization to give a compound of the formula:



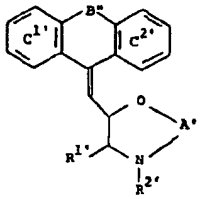
17. A process for preparing morpholine compounds of the formula:



wherein $R^{1'}$, $R^{2'}$, A', $C^{1'}$ and $C^{2'}$ are each as defined in claim 12 and B'' is as defined in claim 13, which process comprises subjecting an alkylaminoalcohol of the formula:



wherein $R^{1'}$, $R^{2'}$, A', B'', $C^{1'}$ and $C^{2'}$ are as defined above to acid-catalyzed rearrangement, followed by intramolecular cyclization to give a compound of the formula:



18. A process as claimed in claim 15 wherein the intramolecular cyclization in reaction (a) is effected by treating the compound of formula (II) with an acid in the presence or absence of an inert solvent.

19. A process as claimed in claim 16 or claim 17 wherein the intramolecular cyclization is effected by treatment with an acid in the presence or absence of an inert solvent.

20. A process as claimed in claim 18 or claim 19 wherein the reaction is effected in the presence of an inert solvent which is acetic acid, chloroform, *n*-hexane, diethyl ether or benzene.

21. A process as claimed in any one of claims 18 to 20 wherein the acid is hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, polyphosphoric, methanesulfonic, benzenesulfonic, toluenesulfonic, oxalic, formic or trifluoroacetic acid or a Lewis acid.

22. A process as claimed in claim 15 wherein the reaction (b) is carried out in an inert solvent in the presence of a base.

23. A process as claimed in claim 22 wherein the inert solvent is benzene, toluene, xylene, diethyl ether, tetrahydrofuran, dioxane, dimethylformamide or dimethylsulfoxide.

24. A process as claimed in claim 22 wherein the base is a metal amide, a metal hydride, or an alkyl or aryl metal.

25. A process as claimed in claim 15 wherein the reaction of the epoxide (V) and the amine (VI) in process step (c) is carried out in an inert solvent in the presence of a base.

26. A process as claimed in claim 25 wherein the inert solvent is methanol, ethanol, isopropanol, ethyleneglycol, diethylether, tetrahydrofuran, dioxane, benzene, toluene, or a mixture of two or more thereof.

27. A process as claimed in claim 25 wherein the base is a metal hydroxide.

28. A process as claimed in claim 15 wherein the reaction (d) is effected using a metal hydride as the reducing agent.

29. A process as claimed in claim 28 wherein the reaction is carried out in an inert solvent.

30. A process as claimed in claim 15 wherein in reaction e(i) the hydrolysis is carried out in an inert solvent in the presence of a base.

31. A process as claimed in claim 15 wherein the reaction (f) is carried out using a palladium-on-charcoal catalyst under an atmosphere of hydrogen gas in an inert solvent.

32. A process as claimed in claim 15 wherein the reaction (g) is effected using a metal hydride as the reducing agent.

33. A process as claimed in claim 32 wherein the reaction is carried out in an inert solvent.

34. A process as claimed in claim 15 wherein the reaction (h) is effected using a metal hydride as the reducing agent.

35. A process as claimed in claim 34 wherein the reaction is carried out in an inert solvent.

36. A process as claimed in claim 15 wherein the reaction (i) is effected in an inert organic solvent in the presence of a base.

37. A process as claimed in claim 36 wherein the inert solvent is benzene, toluene, xylene, dimethylformamide, dimethylsulfoxide, methanol, ethanol or propanol.

38. A process as claimed in claim 36 wherein the base is a metal carbonate, metal bicarbonate, metal hydroxide, metal hydride, alkylamine or metal alkoxide.

39. A process as claimed in claim 15 substantially as hereinbefore described.

40. A compound of Formula I or a non-toxic salt thereof whenever prepared by a process as claimed in any one of claims 15 to 39.

41. A pharmaceutical composition which comprises at least one compound as claimed in any one of claims 1 to 13 or claim 40, or a salt as claimed in claim 14, together with a diluent or carrier.

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